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HEALTH EFFECTS ASSESSMENT FOR HEXACHLOROBUTADIENE

U.S. Environmental Protection Agency
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Office of Health and Environmental Assessment
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Cincinnati, OH 45268

U.S. Environmental Protection Agency
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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A q_1^* was determined for hexachlorobutadiene based on oral exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with hexachlorobutadiene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Hexachlorobutadiene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA-440/5-80-053. NTIS PB 81-117640.

U.S. EPA. 1983a. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Hexachlorobutadiene. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Hexachlorobutadiene was treated as a carcinogen by U.S. EPA (1980a). Limited data are available concerning the carcinogenicity of this compound. In the only study available, oral exposure to hexachlorobutadiene resulted in increased incidence of renal tumors in rats at the highest dose level. No human data are available. U.S. EPA (1980a), using the data for both male and female incidence of renal tubular adenomas and carcinomas in male rats derived a q_1^* for oral exposure of 7.75×10^{-2} $(mg/kg/day)^{-1}$. This risk assessment has been extensively peer reviewed.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
ppm	Parts per million
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of hexachlorobutadiene (CAS No. 87-68-3) are as follows:

Chemical class:	chlorinated aliphatic hydrocarbon	
Molecular weight:	260.72	
Vapor pressure:	0.15 mm Hg at 20°C	Callahan et al., 1979
Water solubility:	2 mg/ℓ at 20°C	Callahan et al., 1979
Log octanol/water partition coefficient:	4.78	Banerjee et al., 1980
BCF:	2.3×10^3	calculated from the equation of Veith et al., 1979
Half-lives in water:	29-2300 3-30 days in river 3-300 days in lakes and groundwater	U.S. EPA, 1980a Zoeteman et al., 1980

No data regarding the half-life of this compound in the atmosphere could be located in the available literature; however, it is likely that the compound will react with hydroxyl radicals in the atmosphere (Singh et al., 1983). In the absence of any rate constant data for this reaction, it is speculated that the half-life of this compound will be several weeks in the atmosphere, based on the estimated residence times for the chlorinated ethylenes given by Singh et al. (1981).

The half-life of hexachlorobutadiene in soils could not be located in the available literature; Based on the expected volatility (Callahan et al., 1979) and biodegradability in aquatic media (Mabey et al., 1981), significant volatilization and biodegradation may not occur in soils.

The compound may, however, be sorbed significantly onto soils containing a high content of organic carbon (U.S. EPA, 1980a). In the absence of significant loss processes, the persistence of hexachlorobutadiene in soil may allow some leaching of the compound into groundwater, particularly from sandy soils.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Pertinent data regarding the absorption of hexachlorobutadiene from the gastrointestinal tract could not be located in the available literature. The available toxicity data indicate that some absorption does occur (Chapter 3) (U.S. EPA, 1980a).

2.2. INHALATION

Pertinent data regarding the absorption of inhaled hexachlorobutadiene could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. The subchronic oral toxicity of hexachlorobutadiene are summarized in Table 3-1. Most of the information is from the Russian literature and is available only as abstracts; therefore, it cannot be fully evaluated.

Kociba et al. (1971) administered diets resulting in doses of 1, 3, 10, 30, 65 or 100 mg hexachlorobutadiene/kg bw/day to female rats for 30 days. The major histopathological change observed was degeneration of the renal tubular epithelium at doses of $\geq$30 mg/kg bw/day. In the 10 mg/kg bw/day group, there was decreased body weight gain with no pathologic alterations. A marginal change in the kidney-to-body weight ratio was observed at 3 mg/kg bw/day and no effects were observed at 1 mg/kg bw/day.

Schwetz et al. (1977) administered diets resulting in doses of 0.2, 2.0 or 20 mg/kg bw/day to male (groups of 10-12) and female (groups of 24) rats for 140 days. Again, histopathological lesions in the kidneys were the major effects noted, occurring at doses of $\geq$2.0 mg/kg bw/day.

3.1.2. Inhalation. The subchronic inhalation toxicity of hexachlorobutadiene is summarized in Table 3-2. Gage (1970) exposed groups of four male and four female rats to atmospheres containing 5, 10, 25 or 100 ppm (53, 107, 267 or 1060 mg/m^3) hexachlorobutadiene, 6 hours/day, for 12-15 days. A dose of 1060 mg/m^3 produced severe toxicity and death. Renal damage was observed in the two highest dose groups, but the only effect observed at an exposure of 107 mg/m^3 was a reduced weight gain in the females. No effects were observed at a concentration of 53 mg/m^3.

TABLE 3-1

Subchronic Oral Toxicity of Hexachlorobutadiene*

Route	Species/ Sex	No. of Animals	% Hexachlorobutadiene Purity	Dose	Duration	Observations	Reference
Oral (diet)	rat/F	4	99	1 mg/kg/day	30 days	No effects.	Kociba et al., 1971
	rat/F	4	99	3 mg/kg/day	30 days	Marginal change in kidney-to-body weight ratio; no pathologic alterations.	
	rat/F	4	99	10 mg/kg/day	30 days	Decreased body weight gain; no pathologic alterations.	
	rat/F	4	99	30 mg/kg/day	30 days	Renal tubular epithelial degeneration, individual cell necrosis and regeneration, decreased body weight gain; increase in mean kidney-to-body weight ratio; increase in hemoglobin concentration.	
	rat/F	4	99	65 mg/kg/day	30 days		
	rat/F	4	99	100 mg/kg/day	30 days		
Oral (diet)	rat/M	12	99	0.2 mg/kg/day	148 days	No effects among adults or neonates.	Schwetz et al., 1977
	rat/F	24	99	0.2 mg/kg/day	148 days	No effects among adults or neonates.	
	rat/M	10	99	2.0 mg/kg/day	148 days	Kidney "roughened," mottled cortex; other kidney changes that normally occur appeared to be accentuated.	
	rat/M	20	99	2.0 mg/kg/day	148 days	Accentuation of normal kidney changes; one had renal lesions identical to those on 20 mg/kg/day; no effects on neonates.	
	rat/M	12	99	20 mg/kg/day	148 days	Change in kidney-to-body weight ratio; kidney roughened with mottled cortex; renal tubular dilation and hypertrophy with foci of renal tubular epithelial degeneration and regeneration.	
	rat/F	24	99	20 mg/kg/day	148 days	Renal tubular dilation and hypertrophy with foci of renal tubular epithelial degeneration and regeneration; decreased values of body and heart weight, increased values for relative weight of brain and kidney; slight decrease in body weight of neonates at time of weaning.	
Oral	rat/NR	NR	NR	0.0005 mg/kg/day	6 months	Was at threshold level with respect to toxicity.	Poteryaeva, 1973
	rat/NR	NR	NR	0.004 mg/kg/day	4 months	Weakly toxic.	
	rat/NR	NR	NR	0.02 mg/kg/day	2 months	Highly toxic.	
Oral	rat/NR	NR	NR	8.4 mg/kg	NR	Severe necrotic nephrosis, as well as abnormal changes in the brain, liver and other internal organs.	Dimitrienko and Vasilos, 1972
				100 mg/kg	NR		

TABLE 3-1 (cont.)

Route	Species/ Sex	No. of Animals	% Hexachlorobutadiene Purity	Dose	Duration	Observations	Reference
Oral	dog/NR	NR	NR	1 mg/kg/day	6 months	Administered to puppies from birth to 6 months. Increased secretion of total N-containing compounds. Increased vol. and total acidity of the gastric juice.	Boranova, 1974a,b
Oral	dog/NR	NR	NR	0.05 mg/kg/day	45 days	Administered 1.5-3 months postnatal; increased total vol., acidity, and amount of HCl and chloride secreted by the stomach.	Kratvitskaya and Boroanova, 1974
Oral	guinea pig/NR	NR	NR	0.004-2 mg/kg/day	7 months	2 mg dose caused a decrease in -SH group conc. in blood plasma without change in blood protein plasma spectrum.	Murzakaev, 1965

*Source: U.S. EPA, 1980a

NR = Not reported

TABLE 3-2

Subchronic Inhalation Toxicity of Hexachlorobutadiene*

Species/ Sex	No. of Animals	% Hexachlorobutadiene Purity	Dose	Duration	Observations	Reference
Rat/NR Mice/NR	NR NR	NR NR	24 mg/m³-air 24 mg/m³-air	7 months 7 months	Caused no alterations.	Gulko et al., 1964
Rat/NR	NR	NR	0.01 mg/m³-air	6 months (5 hours daily)	No effects observed	Poteryaeva, 1972
Rat/M Rat/F	4 4	NR NR	25 ppm (267 mg/m³) 25 ppm (267 mg/m³)	15 daily for 6 hours	Caused respiratory difficulty; decreased weight gain and pathologic injury to the tubular epithelium of the kidneys.	Gage, 1970
Rat/M Rat/F	4 4	NR NR	100 ppm (1060 mg/m³) 100 ppm (1060 mg/m³)	12 daily for 6 hours	Severe toxicity including death.	
Rat/M	4	NR	10 or 5 ppm (107 or 53 mg/m³)	15 daily for 6 hours	Caused no toxicity except for retarded weight gain in females at 10 ppm.	
Rat/F	4	NR	10 or 5 ppm (107 or 53 mg/m³)			

*Source: U.S. EPA, 1980a

NR = Not reported

3.2. CHRONIC

3.2.1. Oral. Kociba et al. (1977a,b) administered diets resulting in doses of 0, 0.2, 2.0 or 20 mg hexachlorobutadiene/kg bw/day to groups of 40 male and 40 female rats for 22-24 months. In the high dose group, body weight gain in both sexes was depressed. Both relative and absolute kidney weights were increased in males and relative kidney weight in females. Survival was decreased in the males. Urinary coproporphyrin excretion was significantly increased in male rats by 12 months and in females by 24 months. Histological examination revealed significant abnormalities, including neoplasms (Section 4.2.1.), in the urinary system.

The effects of 2.0 mg/kg bw/day were much less severe. Urinary coproporphyrin excretion was increased in females after 14 months, and slight histological changes in the kidneys, possibly including renal tubular epithelial hyperplasia, were observed at necropsy. No effects were observed in animals receiving 0.2 mg/kg bw/day.

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of hexachlorobutadiene could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Schwetz et al. (1977) administered diets resulting in doses of 0.2, 2.0 or 20 mg hexachlorobutadiene/kg bw/day for 90 days before mating, 15 days during mating, and throughout gestation and lactation. The only effect on the offspring was a slight decrease in body weight at 21 days postpartum in the high-dose group. No gross malformations were reported and neonatal growth, survival and development were normal in the low- and mid-dose groups.

3.3.2. Inhalation. Pertinent data regarding the teratogenicity or other reproductive effects of inhaled hexachlorobutadiene could not be located in the available literature.

3.3.3. Other. Female rats were given a single 20 mg/kg subcutaneous injection of hexachlorobutadiene prior to breeding (Poteryaeva, 1966). Toxic effects reported in the dams included glomerulonephritis and degenerative red blood cell changes. An increase in neonatal mortality and depressed pup body weights were reported. A lack of detail in the reporting of experimental design and results, combined with poor control pup survival (79%) make this study difficult to evaluate. In addition, this route of administration has limited relevance to the present assessment.

3.4. TOXICANT INTERACTIONS

Murzakaev (1967) reported that treatment with hexachlorobutadiene decreased the sulfhydryl content of blood serum and cerebral cortex homogenate. Mizyukova et al. (1973) subsequently found that administration of thiols (mercaptide, cysteine, "unithiol") 20-30 minutes before a dose of hexachlorobutadiene significantly reduced the resulting toxic effects, as determined by survival rates.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of hexachlorobutadiene in humans could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled hexachlorobutadiene in humans could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Kociba et al. (1977a,b) fed diets resulting in doses of 0, 0.2, 2.0 or 20 mg hexachlorobutadiene/kg bw/day to male and female Sprague-Dawley rats for 2 years (Table 4-1). Total tumor incidences in control and treated groups were similar; however, the incidence of renal tubular neoplasms was significantly increased in both sexes at the highest dose level. No other treatment-related tumors were found.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled hexachlorobutadiene in experimental animals could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Taylor (1978) tested hexachlorobutadiene for mutagenicity in Salmonella typhimurium TA100, both with and without metabolic activation. The low solubility of hexachlorobutadiene limits the interpretation of this test; however, hexachlorobutadiene did not appear to be mutagenic in this system.

4.4. WEIGHT OF EVIDENCE

Data are not available regarding the carcinogenicity of hexachlorobutadiene in humans. The carcinogenicity of this compound has been demonstrated in animals, but only in one strain of rats. Hence, the overall evidence for the carcinogenicity in animals is best designated as "limited." Applying

TABLE 4-1

Response to Hexachlorobutadiene Feeding in Male and Female Rats[a]

Dose[b] (mg/kg/day)	Numbers Male Rat	% Response Male Rat	Numbers Female Rat	% Response Female Rat	Observations
20.0	9/39	23	3/40	7.5	renal tubular adenocarcinomas; undifferentiated carcinoma; metastasis to the lung
2.0	0/40	0	0/40	0	none
0.2	0/40	0	0/40	0	none
Control	1/90	1.1	1/90	1.1	nephroblastoma

[a]Source: Kociba et al., 1977a,b

[b]Dose administered for 669 days of a 730-day experimental period.

the criteria for evaluating the overall weight of evidence for the carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), hexachlorobutadiene is most appropriately designated a Group C chemical - Possible Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1980) has recommended a TLV of 0.02 ppm (~0.24 mg/m^3), based on the 2-year feeding study by Kociba et al. (1977a,b). The U.S. EPA (1980a) estimated that a concentration of 4.47 µg/ℓ in ambient water would result in an increased cancer risk of 10^{-5}.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Hexachlorobutadiene is a chemical shown to be carcinogenic in male rats and for which a q_1^* has been calculated. It is inappropriate, therefore, to calculate an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Hexachlorobutadiene is a chemical shown to be carcinogenic in male rats and for which a q_1^* has been calculated. It is inappropriate, therefore, to calculate an AIC for this chemical.

6.2.1. Inhalation. Pertinent data regarding the chronic inhalation toxicity of hexachlorobutadiene could not be located in the available literature.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Kociba et al. (1977a,b) demonstrated the induction of renal tubular adenomas and carcinomas in rats. The U.S. EPA (1980a), using the tumor incidence in male rats and a linearized multistage model (Table 6-1), has derived a human q_1^* of 7.75×10^{-2} $(mg/kg\ bw/day)^{-1}$.

TABLE 6-1

Basis for q_1^* for Hexachlorobutadiene*

Dose (mg/kg bw/day)	Incidence (No. Responding/No. Tested)
0.0	1/90
0.2	0/40
2.0	0/40
20.0	9/39

Duration of Experiment = 730 days

Length of Treatment = 669 days

Lifespan of Animals = 730 days

Average Weight = 0.610 kg

*Source: U.S. EPA, 1980a

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APPENDIX A

Summary Table for Hexachlorobutadiene

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1^*	Reference
Inhalation				ND	
Oral	rat	0, 0.2, 2.0 or 20 mg/kg bw/day	renal tumors	7.75×10^{-2} $(mg/kg\ bw/day)^{-1}$	Kociba et al., 1971; U.S. EPA, 1980a

ND = Not derived

APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: hexachlorobutadiene

Reference: Kociba et al., 1977a,b

Species, Strain, Sex: rat, Sprague-Dawley, male

Body weight: 0.610 kg (measured)

Length of exposure (le) = 669 days

Length of experiment (Le) = 730 days

Lifespan of animal (L) = 730 days

Tumor site and type: kidney tubules, adenomas and carcinomas

Route, vehicle: oral, diet

Transformed Dose* (mg/kg/day)	Incidence: No. Responding/No. Tested or Examined
0	1/90
0.18	0/40
1.83	0/40
18.33	9/39

*Transformed dose expanded for treatment on 669 of 730-day experimental period.

Unadjusted q_1^* from study = 1.598×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 7.75×10^{-2} $(mg/kg/day)^{-1}$